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| 09/787,033 | 05/14/2001 | Lars Branden | 2921-0128P | 8150 |

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| EXAMINER |
|---|
| NGUYEN, DAVE TRONG |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1632 | 12 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/787,033 | Branden |
| **Examiner** | **Art Unit** |
| Dave Nguyen | 1632 |

*-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☒ Responsive to communication(s) filed on *Nov 4, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above, claim(s) *7, 12, 22, 25, and 27* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-6, 8-11, 13-21, 23, 24, and 26* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicant's election with traverse of Group I claims, claims 1-24 and 26, and species of NLS in the response dated November 4, 2002 is acknowledged. Applicant traverses that Group I and Group II are directed to same class and subclass, and that there is no undue burden to examine both groups. The traversal is not found persuasive because class 14, subclass 44 embraces an enormous number of distinct inventions, and thus, does not preclude a proper restriction between distinct inventions. Claim 27 is written in an ambiguous manner, *e.g.,* "use" claim, without reciting as to what are exactly the process and/or method steps involved in the claim, and as such, it is not apparent as to what exactly applicant is intended to claim. Furthermore, the use of the claimed product in the context of a DNA vaccine is clearly not the same as that in the context of gene therapy. A search of one would not necessarily overlap with that of another.

Therefore, the restriction is proper and made final.

Claims 7, 12, 22, 25, 27 have been withdrawn from further consideration by the Examiner, 37 C.F.R. 1.142(b), as being drawn to a non-elected invention or non-elected species.

Claim 26 is objected because the claims embrace and recite non-elected subject matter.

Claims 1-6, 8-11, 13-21, 23, 24, and 26, to which the following grounds of rejection are applicable, are pending.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24, and 26, readable on a method of transferring a nucleic acid of interest across a direction of a biological membrane to a specific location within or on a cell, are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a method of employing a PNA/FE conjugated to a nucleic acid/carrier to enhance the delivery of a nucleic acid into a cell. While the specification provides sufficient description of a method a method of using the conjugate or complex to deliver a nucleic acid across the cell membrane into a location within a cell, the as-filed specification does not provide sufficient description of a genus of "direction thereof" so as exhibit applicant's intended function of the complex, which is to deliver a nucleic acid to a specific location within or on a cell.

It is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or materials and/or components containing unspecified structures of molecules that are essential for the making the methods as broadly claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of "directions thereof" which are employed in the context of nucleic acid delivery into or onto a cell.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming unspecified molecular structures of "directions thereof" that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the "direction thereof" for use within the context of the claimed invention, which must

exhibit the contemplated biological functions, *e.g.,* an increase in delivery of a nucleic acid to a specific location within or on a cell, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, In view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-24, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A method of delivering a nucleic acid into a target cell comprising the step of using the recited complex or conjugate to deliver a nucleic acid across a cell membrane of the target cell; and

A method of delivering a nucleic acid across the nuclear membrane of a target cell comprising the step of delivering the recited complex or conjugate into the cell, wherein the FE comprises a NLS.

The specification does not reasonably provide enablement for the presently pending claims encompassing any other claimed embodiment, specifically the embodiments embracing the delivery of a nucleic acid across or from any direction to a specific location within or on a cell, nor is the specification enabling for any targeted delivery of any specific location other than the nucleus of any target cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature

of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possessing of the genus of unspecified "direction thereof", particularly in view of the reasons set forth above, one skilled in the art would not known how to use and make the claimed invention so that it would operate as intended.

The claims also encompass a method of introducing a nucleic acid across cell membrane and yet to any specific location on a cell. While it is well-recognized in the prior art, *e.g.,* Verma *et al.* (Nature, Vol. 389, 18, September 1997), that a nucleic acid can be delivered across the cell membrane of a target cell intracellularly, it is not apparent as to how a nucleic acid can be delivered by a carrier such as a plasmid conjugated to a PNA/NLS to a specific location on the surface of a target cell, particularly since the complex is required to go across either the cell membrane or a nuclear membrane of the target cell, and since the as-filed specification does not provide any guidance and/or evidence so as to demonstrate the claimed property within the context of applicant's claimed non-enabling embodiments.

In addition, the claims embrace a method of using any FE to modular delivery of a nucleic acid to any specific location within a cell, *e.g.,* mitochondria, golgi complexes. However, the specification coupled with the knowledge in the art does not provide sufficient guidance as to how a skilled artisan uses the claimed method to modulate targeted delivery of any nucleic acid to any specific location within a target cell *in vitro* and/or *in vivo* so as to provide a beneficial effect, without undue experimentation, particularly on the basis of applicant's disclosure. While NLS are well-known in the art as a facilitator to enhance the delivery of a nucleic acid across the nuclear membrane into the nucleus of a target cell, there is no indicated specific guidance as to how any other FE can be employed to exhibit the claimed 's properties, *in vivo* delivery of a nucleic acid into any specific location of a target cell from any tissue. In order to practice the claimed invention , a skilled artisan would turn to the specification for guidance as to what is exactly the FE so as to carry out the targeted delivery of any location within a target cell.

However, the specification appears to disclose sufficient guidance only as to the use of a NLS as the FE to carry a nucleic acid across the nuclear membrane of a target cell. Next, there is no disclosure from the as-filed specification of any component of FE that is or is to be used to modulate the targeted delivery of a nucleic acid into any specific location other than the nucleus and/or cytoplasm of a target cell. Thus, the specification lacks sufficient guidance and/or description and/or factual evidence demonstrating as to how a skilled artisan practices the introduction of any nucleic acid to any specific location of any target cell *in vitro* and/or *in vivo* so as to produce a beneficial effect within the context of applicant's claimed invention, particularly on the basis of applicant's disclosure. The specification does not provide guidance and/or description of any and/or all other sited directing molecules to transfer the delivery of a substance inside in the cytosol of a target cell to any other specific cellular target location. Thus, it is not apparent as to how one skilled in the art to determines, without undue experimentation, as to which of the other FE would exhibit the function as recited in the claim, particularly on the basis of applicant's disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112, second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the application regards as his invention.

Claims 1, 10, 11, 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 10 embrace the recitation of "each as in HIV protein, and claims 1, 10, 15, 24 recite the e.g.,", which renders the claims indefinite. The "e.g" does not indicate *per se* as to what are exactly included or excluded from the intended breadth of the "protein". The "each as in" is ambiguous and is not necessarily the same the limitation of a HIV protein which enables

both membrane translocation and nuclear transport of the nucleic acid of interest.

Claims 11 and 13, 15, 23, 24 are indefinite in the recitation of the "such as" because "such as" does not clearly indicate *per se* as to what are exactly included or excluded from the intended breadth of the claims.

Claim 26 claims the use of a nucleic acid complex including a PNA and a PNA target contained in a nucleic acid of the complex, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method, process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 26 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki,* 153 USQP 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner,* 255 F. Supp. 131, 149 USPQ 475 (D.D.C., 1966).

Claims 2-6, 8-10, 13, 14, 16-21, 23, 24 are objected in the recitation of the article "A" in the beginning of the claim. A dependent claim must refers to the base claim by reciting "The" rather than "A" in order to comply with US patent standard should the claims be issued in a US patent.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in (1) an application for patent, published under section

122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-11, 13-21, 23, 24, and 26 are rejected under 35 USC 102(e), as being anticipated by, or the alternative under 35 USC 103(a), as being unpatentable over Felgner (US Pat No. 6,165,720).

Felgner teaches a nucleic acid delivery complex comprising essentially the same as claimed: a PNA operably linked to a NLS, which in turn is further operably linked to nucleic acid containing a PNA target to which the PNA hybridizes, *e.g.,* abstract, entire columns 3 and 4, particularly column 3 bridging column 4, column 7, columns 11 and 12. A modified PNA, which

comprises a marker is also taught in column 3, lines 35-45. An embodiment wherein the linkers are disclosed so as to conjugate any of the essential components in the nucleic acid delivery composition is also disclosed on column 12. Methods of using the complex so as to enhance the delivery of the nucleic acid into the nucleus of a target cell is also disclosed on columns 7 and 8. Methods of using the delivery complex so as to deliver the nucleic acid to any target cell *in vitro* and/or *in vivo* are also disclosed on column 11, lines 45-60.

To the extent that the claims embrace a target cell comprising a cell wall or any other minor modifications which include the nature of spacers and/or linkers, it would have been obvious for one of ordinary skill in the art to have employed minor modification and/or as a matter of design choice to employed the complex to enhance the delivery and monitory of the distribution intracellularly in any cell of desire including those having a cell wall, particularly since the level of one ordinary skill in the art is relatively high, and since Felgner teaches that the complex when employed in any cell delivery method would enhance the entry of a desire nucleic acid into any target cell *in vitro* and/or *in vivo,* and would further facilitate the study and understanding of the cellular and molecular barriers to DNA delivery and the distribution of the delivered DNA intracellularly (columns 3-5, 10).

Thus, the claimed invention is anticipatory, or in the alternative, as a whole was *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds* may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner

DAVE T. NGUYEN
PRIMARY EXAMINER